Statistical Analysis Plan (SAP)

Sponsor:	Octapharma
Study Title:	Prospective, multinational, non-interventional post-authorisation study to document the long-term immunogenicity, safety, and efficacy of Human-cl rhFVIII (simoctocog alfa) in patients with haemophilia A treated in routine clinical practice
Protocol Version/Date:	Ver. 5.0; 2017-09-26
SAP Version/Date:	Ver. 2.0; 2020-10-30
Supersedes SAP Version:	Ver. 1.0; 2020-02-05
Appendices (external documents):	1. List of Tables, Listing, Figures (TLFs)

Approval

The Trial Statistician hereby confirms that the SAP was prepared in conformance with the procedures and principles set forth in the indicated protocol version and all established relevant guidelines.

Name Affiliation, Function	Signature:	Date:
[redacted]		

By signing hereafter, I confirm that this Statistical Analysis Plan adequately describes the statistical analyses to be performed in the context of this study.

Name Affiliation, Function	Signature:	Date:
[redacted]		

Name **Affiliation, Function**	**Signature:**	**Date:**
[redacted]		
[redacted]		

Revision history

SAP Version	Version date	Reason(s) for change
1.0	2020-02-05	First version
2.0	2020-10-30	Description of derivation for annualized bleeding rate modified and for monthly bleeding rate added. Data under on-demand regimen will only be listed. The prophylactic phase(s) of patients switching between prophylactic and on-demand regimen will be included in analysis. Further minor changes

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LIST OF ABBREVIATIONS

Abbreviation	Description
ABR	Annualised Bleeding Rate
ADR	Adverse Drug Reaction
BE	Bleeding Episode
BW	Body Weight
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DD	Drug Dictionary (WHO Coding Thesaurus)
DMP	Data Management Plan
DRM	Data Review Meeting
ED	Exposure Day
FAS	Full Analysis Set
FVIII	Coagulation Factor VIII
FVIII:C	Factor VIII-coagulant
ICF	Informed Consent Form
ID	Identifier
ITT	Intention-To-Treat
IU	International Unit
IV	Intravenous
IVR	Incremental in Vivo Recovery
LOCF	Last Observation Carried Forward
MBR	Monthly Bleeding Rate
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of Patients/Observations
POP	Postoperative
PP	Per-Protocol
PT	Preferred Term
PTP	Previously Treated Patients
QC	Quality Control
SABR	Spontaneous Annualized Bleeding Rate
SADR	Serious Adverse Drug Reaction
SMBR	Spontaneous Monthly Bleeding Rate
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software package
SD	Standard Deviation
SOC	System Organ Class
SP	Statistical Programmer
SURG	Surgery analysis set
TABR	Total Annualized Bleeding Rate
TEADR	Treatment Emergent Adverse Drug Reaction
TLFs	Tables, Listings, Figures
TRABR	Traumatic Annualized Bleeding Rate

Abbreviation	Description
TRMBR	Traumatic Monthly Bleeding Rate
TS	Trial Statistician
WHO	World Health Organization

1 STUDY INFORMATION

1.1 Overall objective

The overall objective of this study is to collect clinical data in addition to those obtained during the clinical study program and to ensure the consistency, in the long-term, between the outcome from pre-authorisation clinical studies (in 135 previously treated paediatric and adult patients) and routine clinical practice.

In addition to general product safety and efficacy, the focus of this study will be on immunogenicity, particularly on inhibitor development.

The objectives of this study are:

- To assess the long-term immunogenicity and safety of Nuwiq® [Human-cl rhFVIII (simoctocog alfa)] in treating or preventing bleeding episodes (BEs) in patients with haemophilia A
- To assess the long-term efficacy of Nuwiq® in treating or preventing BEs in patients with haemophilia A

1.2 Study design

This is a prospective, multinational, non-interventional post-authorisation study designed to assess the long-term immunogenicity, safety, and efficacy of Nuwiq® in patients with haemophilia A treated in routine clinical practice.

1.3 Planned sample size

The sample size of the study was not based on statistical reasoning, but was chosen according to regulatory recommendations for post-authorisation studies as outlined in the 'Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products' by the European Medicines Agency (EMA), EMA/CHMP/BPWP/144533/2009. Therefore it is planned to enrol 200 haemophilia A patients (FVIII:C ≤ 2%).with the following restrictions:

- Of the 200 enrolled patients, at least 100 patients should have severe haemophilia A (FVIII:C < 1%).
- Because the results of a clinical study in children was evaluated as part of the marketing authorisation procedure, patients of every age group are eligible to be included in this study. The age distribution of enrolled patients should be evenly balanced. Thus, of the 200 enrolled patients, approx. 60 patients should be < 12 years of age. Also, at least 10 patients should be aged between 14–18 years.
- Patients with severe haemophilia A after successful immune tolerance induction (ITI) can also be included; the proportion of these ITI patients should not exceed 25% of the entire cohort.

2 GENERAL INFORMATION

2.1 Background details

All study data will be transferred to a SAS database (version 9.4 or later) for statistical analysis purposes. Data will be imported from the Data Capture System OPVerdi via validated SAS programs. If applicable, external data will also be transferred to SAS for presentation of these data in the statistical analyses.

The SAP will be finalized before the first analysis after agreement with the Sponsor.

2.2 Deviations from the trial protocol with regard to statistical analyses

No deviations from the descriptive statistical methods stated in the protocol are planned.

2.3 Individual protocol deviations

No specific protocol deviations will be considered as this is a non-interventional study. However, in order to present the results for the targeted study cohort the occurrence of any of the following events may be considered for exclusion of a patient from the Per Protocol (PP) set:

- Violation of in-/exclusion criteria,
- Factor replacement treatment with a different product than Nuwiq®,
- Insufficient documentation of administration data,
- Less than 100 exposure days (EDs).

A detailed review of all documented and derived deviations from protocol will be part of the DRM before database lock. During this DRM the impact of protocol deviations on the analysis will be assessed and the conclusions recorded.

A complete listing of documented and derived protocol deviations and the judgment for assessment of patient disposition will be signed before database lock. A description of protocol violations that led to exclusion from any analysis sets will be included in the table part of the CSR.

3 ANALYSIS POPULATIONS

The disposition of patients will be displayed according to the following analysis populations:

- Safety (SAF) population
- Full Analysis Set (FAS)
- Per Protocol (PP) set
- Surgery (SURG) set

Membership of patients will be decided upon in a DRM with the Sponsor before database lock. The proper flags for analysis sets exclusion (e.g., exclusion from SAF set), will be included in the analysis datasets. The protocol deviation list should be finalized before database lock.

3.1 Safety Population

The safety (SAF) population will include all patients who received at least one infusion with Nuwiq®.

3.2 Full Analysis Set

The **full analysis set (FAS)** is based on the intention-to-treat principle and will include all enrolled patients who received at least one infusion of Nuwiq® and for whom at least one measurement after first infusion is available.

3.3 Per Protocol (PP) Set

The **Per Protocol set (PP)** will include all patients of the FAS without important deviations from the protocol.

3.4 Surgery Set

The **surgery set (SURG)** will be a subset of the FAS, containing all patients who underwent a surgical procedure treated with Nuwiq®.

3.5 Subgroup analyses

Selected efficacy parameters (e.g. statistics on ABR, substance use and bleeding episodes) will be presented for the categories of the following two subgroups

- Age:
  - <12 years,
  - 12 – <18 years
  - ≥18 years
- Severity of haemophilia, as based on the residual FVIII:C level at screening:
  - Moderate (1% < FVIII:C ≤ 2%)
  - Severe (FVIII:C ≤ 1%)

4 STATISTICAL ANALYSES

All statistical analyses will be performed using the SAS® software (Version 9.4 or later).

The analysis of safety will be based on the SAF set. The evaluation of overall efficacy will be performed on the FAS and PP set.

Analysis of the efficacy and safety of Nuwiq® in surgeries will be based on the SURG set.

If not stated otherwise the following standard descriptive statistics will be presented:

- Descriptive statistics for continuous data

  N, mean, SD, min, lower quartile, median, upper quartile and max will be presented. These descriptive statistics will be determined for measured values and optionally for differences to baseline.

- Descriptive statistics for categorical data

  Absolute frequencies and percentages will be presented. Percentage bases (denominators) will be identified in the table title or footnote (i.e. all patients at risk, all non-missing cases, all cases). For changes from baseline, shift tables may be generated.

- Exploratory statistics

  Although statistical methods are primarily descriptive, two-sided 95% confidence intervals may be presented for selected parameters (e.g. incidences of adverse drug reactions, annualized bleeding rate) in an exploratory manner.

- Listings

  All recorded data will be listed by patient. Identification variable will be the patient ID.

  Derived data will be stored in special analysis data sets and will be calculated as outlined in section 6.1.

4.1 Conventions

4.1.1 Baseline definition

Assessments at or before screening visit will be considered as baseline.

4.1.2 Missing data

In case of missing body weight (BW) documentation data will be imputed using the Last Observation Carried Forward (LOCF) approach to calculate the dose per kg BW(IU/kg).

No further imputations for missing data will be performed.

Calculations pertaining to the derivation of annual bleeding rates will be based on documented time periods only.

4.1.3 Pooling of centres

All tables will be presented in total over all participating countries and centres. The distribution of number of patients per country will be presented in the disposition section of the report. No pooling of centres will be performed.

4.2 Demographic and other background data

4.2.1 Basic description

All available demographic and anamnestic data will be summarised in appropriate tables (summary statistics or frequency tables) for the FAS and PP population.

4.2.2 Homogeneity tests

Not applicable.

4.3 Nuwiq® exposure, compliance

Each administration of Nuwiq® including all treatment details will be listed.

4.4 Medical history

Details of medical history findings will be listed by subject.

4.5 Prior and concomitant medication

Medications will be coded using the WHO Drug Global thesaurus in the version current at the time of database lock. Coding will be performed by the CRO and agreed upon with the sponsor before database lock. (cf. DMP). For concomitant medications tables will show the frequencies of patients by WHO preferred term. Prior medication will only be listed.

4.6 Efficacy

The study objective of assessing the long-term efficacy of *Nuwiq*® will be evaluated using the following outcome parameters:

- Annualised rate of bleeding episodes (BEs)
- FVIII consumption data
- Number of EDs
- Number of infusions (needed to treat a breakthrough BE)
- FVIII IU/kg per infusion, per BE, per month, per year

The efficacy analysis will be performed for patients under prophylactic regimen. This includes all phases under prophylactic treatment according to the prescribed schedule at visits. Data for patients under on-demand regimen will only be listed. For patients switching

between on-demand and prophylactic regimen the prophylactic treatment phase will be included in efficacy analysis whereas data under on-demand phase will only be listed. The analysis of the above listed outcome parameters will be stratified by severity of Haemophilia A (severe and moderate).

The efficacy in treatment of bleeding episodes will be evaluated by descriptive statistics for the following parameters:

- Basic bleeding characteristics including site, cause and severity
- Total number and frequency of bleeding episodes (spontaneous, traumatic, other) during the study
- Frequency of bleeding episodes per year
- Overall efficacy rating
- Frequency of successfully treated bleeding episodes (excellent and good efficacy rating,
- The number of infusions needed to treat a BE, the number of EDs and study drug consumption data (Nuwiq® IU/kg per infusion, per ED and BE) per subject and in total will be evaluated

The analysis of the efficacy of treatment with Nuwiq® will be based on the FAS.

Primarily, all obtained data on treatment characteristics (Nuwiq® dosages, frequencies, total consumption) and BEs (duration, frequency, efficacy assessment) will be described by providing appropriate summary statistics.

4.7 Short-form health survey SF-36

Analysis of the optional SF-36 documentation will comprise summary statistics for the derived scores. Summary tables will be provided for screening (i.e. baseline) and after 100 EDs visit including changes to baseline.

4.8 Surgeries

Efficacy in surgical prophylaxis will be analysed descriptively, presenting summary tables and listing on all aspects of surgical treatment and procedures as well as efficacy ratings.

- Details of the surgical intervention
- Number of surgeries by severity category (minor, major, total)
- Details on treatment for surgical prophylaxis (number of exposure days and injections prior to surgery, dosing details, total amount of Nuwiq®
- Details on treatment with Nuwiq® pre-, intra- and post-operatively (number of exposure days and injections, dosing details, total amount of Nuwiq®)
- Evaluation of blood loss and hematomas

- Use of blood and blood product transfusions, including any blood or blood product transfusions or colloidal plasma substitutes (such as albumin, hydroxyl starch, dextran, and gelatine)
- Overall haemostatic efficacy evaluation at the end of surgical treatment period.
- FVIII plasma levels in the context of the surgery

All analyses of surgical efficacy will be based on the SURG population.

4.9 Safety

All safety analyses will be based on the SAF population.

The analysis of safety will include the occurrence of ADRs, and immunogenicity measurements (Factor VIII inhibitor).

4.9.1 Adverse Drug Reactions

Adverse Drug Reactions (ADRs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Coding will be agreed upon with the Sponsor before database lock (cf. DMP).

All ADRs recorded since signing of the informed consent form (ICF) will be listed in the appendix of the study report.

The statistical analysis will include all documented ADRs that started or worsened after the start of Nuwiq® infusion. It is assumed that for each increase in intensity of an ADR a new entry of the ADR will be done by the investigator; hence such cases will be analysed like different phases of the same ADR.

A descriptive analysis will be performed. Total number of ADRs and incidences, along with 95% confidence intervals, will be presented by primary system organ classes (SOC) and incidences of PT within primary SOC sorted according to the Internationally Agreed Order.

Multiple counts within a PT or SOC (repeated or different included terms or changes in descriptors) will be counted only once for the calculation of incidences.

Global incidences will be calculated for:

- All ADR
- ADRs by worst severity
- Serious ADRs

A listing of "special cases" containing patient identification, age, ADR descriptors, start and end of treatment will be prepared for the following types of ADRs:

- Serious ADRs (SADR)
- ADRs which led to death
- ADRs which led to discontinuation

- FVIII inhibitor occurrences
- Hypersensitivity reactions
- Thromboembolic events

Incidence tables for these events will also include 95% Pearson-Clopper CIs.

4.9.2 Laboratory variables

The analysis of specific lab parameters (FVIII inhibitors, FVIII concentrations) will be purely descriptive and presented as summary tables or listings. Laboratory data obtained in context of surgeries will only be listed.

4.10 Other variables

Not applicable.

4.11 Interim analyses

Not applicable.

5 QUALITY CONTROL

The SAP was reviewed by the trial statistician (TS) before signature. Particularly the TS has checked the consistency of the described methods and outputs with the actual version of the study protocol. In addition, a sponsor representative has reviewed the SAP before final approval.

Log files of all SAS® programs used in the analysis will be checked for errors, warnings and suspicious notes by the statistical programmer (SP). All findings will be either eliminated or commented upon. The final version of each program will be stored along with its log file in the electronic archive.

All programs will be validated by the program author or an independent statistical programmer depending on the requested validation level selected in the List of TLFs.

The agreement of the program outputs with the SAP, their consistency and plausibility will be checked by the TS. Moreover, the TS will review the outputs regarding completeness, readability and comprehensibility.

The described process is associated with the 'normal' level of program validation. Additional levels of quality control can be specified in the List of TLFs (see Appendix, 1) for individual outputs.

6 DERIVATIONS AND TRANSFORMATIONS

6.1 Formulas for derived variables

Variable	Definition / Derivation
Durations between two dates	Later date minus earlier date plus 1, expressed in days. (Remark: Duration will be 1, if both dates are the same.)
Annualized bleeding rate	Number of bleedings under prophylactic phase / (duration of prophylactic phase)/365.25. Only patients with at least 3 month of prophylactic treatment will be included in analysis of ABR Will be calculated for total, spontaneous and traumatic bleedings (TABR, SABR, TRABR).
Monthly bleeding rate	Number of bleedings / (duration of prophylactic phase/365.25*12. Only patients with at least 3 month of prophylactic treatment will be included in analysis of MBR Will be calculated for total, spontaneous and traumatic bleedings (TMBR, SMBR, TRMBR)
ED	Exposure day = each day the patient received Nuwiq®
Success (for bleeding episodes and surgeries)	Excellent or good efficacy rating
Prophylactic phase	Subjects under prophylactic schedule during whole study: prophylactic phase = last date of Nuwiq® – first date of Nuwiq® + 1)/365.25. Subjects switching between on-demand and prophylactic schedule: all phases under planned regimen “Prophylaxis” according to documented schedule at visits will be summarized. The start of prophylactic phase either corresponds to the date of first treatment with Nuwiq® (if prophylactic regimen is pre-scribed at screening) or the documented start date of prophylactic regimen at visit. In case of a switch from prophylactic to on-demand regimen the last prophylactic treatment before switch to on-demand schedule will be taken as end of prophylactic phase. In case of prophylactic schedule before end of study the last date of Nuwiq® marks the end of prophylactic phase.
On-demand phase	Subjects under on-demand schedule during whole study: date of study completion – date of screening + 1)/365.25. Subjects switching between on-demand and prophylactic schedule: all phases under planned regimen “On-Demand” according to documented schedule at visits will be summarized. The start of on-demand phase either corresponds to the date of screening (if on-demand schedule is pre-scribed at screening) or the documented start date of on-demand regimen at visit. In case of a switch from on-demand to prophylactic regimen the day before first prophylactic treatment under new schedule will be taken as end of on-demand phase. In case patient is on on-demand regimen at last visit before completion the date of study completion will be taken as end of on-demand phase.

Variable	Definition / Derivation
Average Nuwiq® consumption under on-demand regimen	Consumption per week: total dose in on-demand phase/(on-demand phase (days) / 7) Consumption per months: total dose in on-demand phase/(on-demand phase (days) / 365.25*12)
Average Nuwiq® consumption under prophylactic regimen	Consumption per week: total dose in prophylactic phase / (prophylactic (days) / 7) Consumption per months: total dose under prophylactic phase / (prophylactic phase (days) / 365.25*12)

6.2 Transformations to be applied

Not applicable.

7 REFERENCES

No specific references were used.

APPENDICES

1. List of Tables, Listings, Figures

A complete List of tables, listings, figures (TLFs) will be given in a separate document which can be updated without updating the SAP. The List will serve as a reference for the Sponsor, the TS and the SP and describes the entire set of statistical output to be produced. Therefore, this List will be versioned and approved by both Ergomed and Sponsor before commencing the statistical programming.

Each output page will have an appropriate heading specifying the study ID and abbreviated study title.

Each output page will show a common date and page numbers in the form 'Page [x / y]' where x denotes the current page within an output and y the total number of pages of that output. The output pages will not contain any other sequential page numbering.

All statistical output will identify the underlying analysis set(s) and indicate the number of patients/events in this set (N) and the number of patients/events actually contributing to the particular output (n).

All patient listings will contain in addition to the patient identification the analysis set.